Palmoplantar Keratoderma With Progressive Gingivitis and Recurrent Pyodermas

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Practice Points

- Papillon-Lefèvre syndrome (PLS) is an autosomal-recessive inherited transgredient palmoplantar keratoderma (PPK) that is associated with gingivitis and recurrent pyodermas.
- The symptoms associated with PLS are thought to be due to cathepsin C gene, *CTSC*, mutations. *CTSC* is expressed in epithelial regions commonly affected by PLS and also plays a role in the activation of immune and inflammatory responses.
- Papillon-Lefèvre syndrome must be differentiated from other conditions causing PPK, such as Haim-Munk syndrome, Greither syndrome, mal de Meleda, Clouston syndrome, Vohwinkel syndrome, and Olmsted syndrome.
- Treatment of PLS includes keratolytics such as urea and/or salicylic acid combined with oral retinoids. Active gingivitis may be treated with combined use of amoxicillin and metronidazole.

Papillon-Lefèvre syndrome (PLS) is a rare inherited palmoplantar keratoderma (PPK) that is associated with progressive gingivitis and recurrent pyodermas. We present a case exhibiting classic features of this autosomal-recessive condition and review the current understanding of its pathophysiology, diagnosis, and treatment. Additionally, a review of pertinent transgredient PPKs is undertaken, with key and distinguishing features of each syndrome highlighted.

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Case Report

A 30-year-old woman presented to the dermatology clinic with erythematous hyperkeratotic plaques on the palms and soles. The plaques extended onto the dorsal aspects of the fingers, toes, hands, and feet (Figures 1 and 2). The patient had psoriasiform plaques on the extensor surfaces of the knees and elbows (Figure 3) along with a history of slow-progressing gingivitis and periodontal disease that began in early childhood (Figure 4). The patient also had modest hyperhidrosis of the palms and soles, several scattered longitudinal grooves of the nails, and a history of chronic furunculosis with occasional abscesses requiring incision and drainage. There were no notable hair findings. The patient was otherwise healthy with normal neurologic development.

Comment

Papillon-Lefèvre syndrome (PLS) is an inherited palmoplantar keratoderma (PPK) characterized by a diffuse transgredient palmoplantar hyperkeratosis and associated periodontitis with resultant premature loss of teeth. Papillon and Lefèvre[1] first recognized this condition as a distinct entity in their 1924 report of a brother and sister who

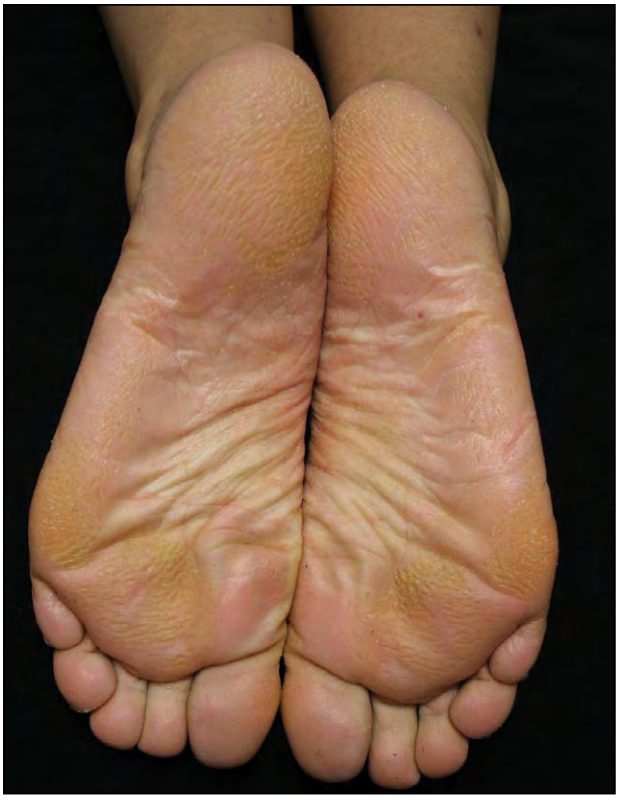

Figure 1. Diffuse palmoplantar keratoderma.

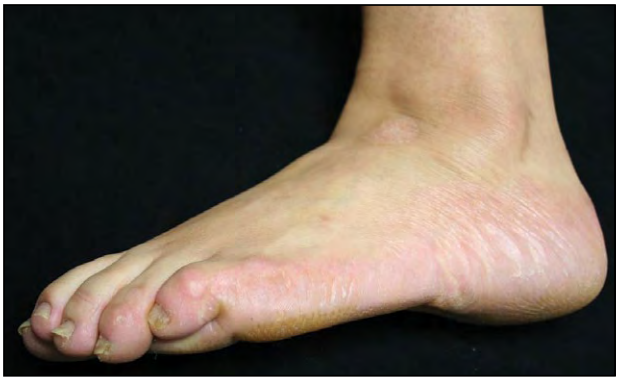

Figure 2. Lateral view of the foot showing transgrediens.

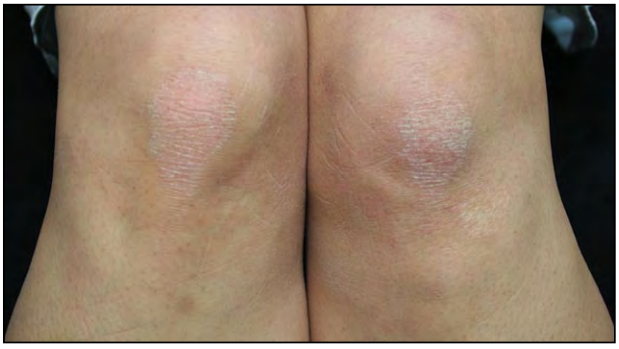

Figure 3. Psoriasiform plaques on the extensor surfaces of the bilateral knees.

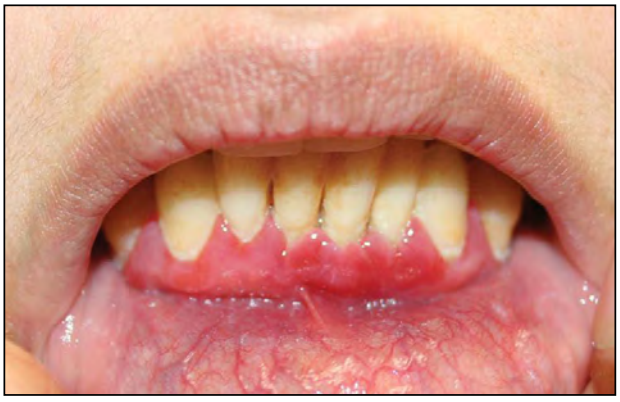

Figure 4. Periodontal disease associated with palmoplantar keratoderma.

demonstrated the distinguishing characteristics of the disease. Papillon-Lefèvre syndrome is inherited in an autosomal-recessive pattern, with equal penetrance in males and females and without racial predominance.[2] The disease is rare, with a prevalence estimated to be 1 to 4 per million individuals in the general population; the carrier rate is estimated to be 2 to 4 per 1000 individuals.[3]

Palmoplantar keratoderma in PLS usually arises within the first 4 years of life. The keratotic plaques most often involve the entire surface of the palms and soles but also can occur focally.[4] Palmoplantar keratoderma may be exacerbated in the cool dry winter months during which patients sometimes develop painful fissures.[5] Psoriasiform plaques on the elbows and knees and hyperhidrosis of the palms and soles often are evident.[6,7] Nail changes that manifest as transverse grooves and fissures typically are apparent in advanced cases. Additional cutaneous findings include recurrent pyogenic infections of the skin, which occur in approximately 20% of patients with PLS.[8,9] Histopathologic findings of the palmoplantar skin of patients with PLS are relatively nonspecific and not well described in the literature. Reported findings include hyperkeratosis, acanthosis, thinned dermal papillae with tortuous capillaries, and occasional patches of parakeratosis. A slight perivascular inflammatory infiltrate also has been described.[10,11]

Although teeth erupt normally in patients with PLS, their eruption is accompanied by gingival inflammation and subsequent destruction of the periodontia, with resultant characteristic loss of deciduous and permanent teeth. Involvement of the dentition appears at 3 to 4 years of age, with some patients becoming edentulous by early adolescence,

except for typical sparing of the third molars.[12,13] Premature loss of teeth may lead to distortion of maxillary and mandibular bone growth.[14] Notably, there appears to be no correlation between the degree of dermatologic involvement and severity of periodontal disease.[15]

Recurrent pyodermas also are relatively common in PLS, likely related to a loss of function of various immune cells. Impairment of chemotaxis as well as excessive production of free radicals and polymorphonuclear leukocytes frequently are noted in PLS patients.[16,17] Further described derangements include alteration of natural killer cell cytotoxic function and reduction in T lymphocyte levels.[18,19] Infections resulting from these immunologic impairments are varied and include cutaneous pyodermas and furunculosis, periodontitis, and pneumonia. Even fatal infections such as abdominal abscesses have been reported, with increasing reports of pyogenic hepatic abscesses as a complication of PLS. Bacteremia during periods of extensive periodontal inflammation also is known to occur.[20,21]

Several variants of PLS have been reported, including cases of late-onset PLS, rare associations with oculocutaneous albinism, acro-osteolysis, pseudoainhum, and ocular surface squamous neoplasia.[22-26]

The unique constellation of symptoms associated with PLS is thought to stem from mutations in the cathepsin C gene, *CTSC*, on 11q14. *CTSC*, also known as dipeptidyl peptidase I, plays an important role in intracellular protein degradation and functions as a central coordinator for activation of many serine proteases that are critical to the immune and inflammatory responses of myeloid and lymphoid cells.[27] Loss of *CTSC* activity thus may help to explain the variety of immunologic defects seen accompanying transgredient PPK and gingivitis in patients with PLS. Specifically, defects in *CTSC* lead to reductions in the levels and activities of the neutrophil-derived serine proteases cathepsin G, neutrophil elastase, and proteinase 3. These losses are clinically important, as these serine proteases, along with antimicrobial peptides, form the basis of the oxygen-independent processes that neutrophils use to kill bacteria, particularly *Actinobacillus actinomycetemcomitans*, a bacterium commonly implicated in the pathogenesis of periodontitis.[28] Additionally, *CTSC* is essential for optimal activation and stability of granzymes A and B, which are required for T cell–mediated cell killing.[29] The inactivation of granzyme B in natural killer cells leads to a failure to induce the proapoptotic caspase cascade in target cells; normal caspase function plays an essential role in programmed cell death, necrosis, and inflammation.[30]

Interestingly, it also is thought that *CTSC* defects play a role in the hyperkeratosis seen in PLS patients. *CTSC* is expressed in epithelial regions commonly affected by PLS, such as the palms, soles, knees, and keratinized oral gingiva. It functions in the regulation of proteolysis in epithelia, and when this proteolysis is disturbed, abnormal cornification and cell turnover result. Thus *CTSC* has been proposed as essential for establishing and maintaining the structural organization of the epidermis in the extremities as well as the integrity of the tissue surrounding the teeth; it also may contribute to the processing of proteins such as keratins.[31]

The clinical differential diagnosis for PLS includes other transgredient PPKs, chiefly Haim-Munk syndrome. Patients with Haim-Munk syndrome present similar to those with PLS with diffuse PPK plus periodontitis; however, they also have arachnodactyly, acro-osteolysis, and atrophic nail changes. Haim-Munk syndrome also is the result of mutations in *CTSC* and is considered to be an allelic variant of PLS.[32]

Additional PPK considerations, listed in roughly descending order of clinical relevance, include Greither syndrome, mal de Meleda, Clouston syndrome (hidrotic ectodermal dysplasia), Vohwinkel syndrome, and Olmsted syndrome (Table). Greither syndrome, also known as transgrediens et progrediens PPK, manifests with similar cutaneous findings as PLS, with a transgredient PPK and hyperkeratosis of the knees and elbows; however, no extracutaneous features are evident. Greither syndrome is caused by mutations in the keratin 1 gene, *KRT1*, and has an autosomal dominant mode of inheritance.[33] Mal de Meleda has an autosomal-recessive inheritance pattern and may be distinguished by a malodor of the feet and constricting bands on the terminal phalanges. Clouston syndrome, which is autosomal dominant, is characterized by tufted phalanges in addition to a transgredient PPK; it has no associated hyperhidrosis. Vohwinkel syndrome is distinguished by starfishlike keratoses and ainhumlike constricting bands; it is clinically distinctive and unlikely to be confused with PLS. Finally, Olmsted syndrome is a rare disorder characterized by mutilating PPK with periorificial keratotic plaques as well as flexion contractures.[34]

The histologic differential diagnosis is similar to the clinical differential, with histologic features being nonspecific but allowing for differentiation from epidermolytic hyperkeratosis–associated PPKs. Clinicopathologic correlation is essential to making an accurate diagnosis, as distinction among the nonepidermolytic PPKs on histopathologic grounds alone often is not possible. Epidermolytic PPK disorders, such as bullous ichthyosis, are distinguished from the nonepidermolytic PPKs by compact

Pertinent Features of Transgredient PPKs

Diagnosis	Features	PPK Pattern
Papillon-Lefèvre syndrome	Periodontal disease, recurrent pyodermas	Transgredient PPK
Haim-Munk syndrome	Acro-osteolysis, arachnodactyly, nail dystrophy, periodontal disease	Transgredient PPK
Greither syndrome	Hyperhidrosis	Transgredient PPK involving knees/elbows more than palms/soles
Mal de Meleda	Fetid odor, hyperhidrosis, pseudo-ainhum	Transgredient PPK with sharp cutoff at wrists and ankles
Clouston syndrome	Nail dystrophy, paronychial infections, sparse hair, tufted terminal phalanges	Transgredient PPK
Vohwinkel syndrome	Ainhumlike bands of constriction on digits, honeycomb-patterned keratoderma, starfish-shaped keratoses of the dorsal digits, subset with sensorineural deafness	Transgredient PPK
Olmsted syndrome	Oral leukokeratosis, periorificial keratoderma, painful flexion contractures	Mutilating transgredient PPK

Abbreviation: PPK, palmoplantar keratoderma.

hyperkeratosis and accompanying granular and vacuolar degeneration of the spinous and granular cell layers; nonepidermolytic PPKs have prominent orthokeratotic hyperkeratosis with focal parakeratosis and thickened granular layer but no vacuolar or granular degeneration.[34]

Treatment of PLS is similar to other PPKs, with varying degrees of improvement of PPK symptoms with oral retinoids and emollients, often coupled with urea and/or salicylic acid. Additionally, prolonged use of oral retinoids has been associated with improvement of periodontal disease and prevention of tooth loss. A reasonable starting regimen would be acitretin (0.4–1 mg/kg per day); gradual tapering may be possible once symptoms resolve.[35,36] Further treatment of periodontitis includes extraction of primary teeth combined with oral antibiotics and regular teeth cleaning. Antibiotics during periods of active gingivitis may help preserve teeth and prevent bacteremia as well as the subsequent development of pyodermas and hepatic abscesses. The current literature supports the combined use of amoxicillin and metronidazole, each at 250 mg 3 times daily for 20 days during periods of active gingivitis.[37] Use of prophylactic antibiotics to prevent systemic infections in patients with PLS has not been studied, and no established guidelines exist dictating how to address concern for recurrent infections and associated immunodeficiency.[21]

Conclusion

Patients presenting with transgredient PPK should be evaluated for a history of periodontitis and infections, both associated with PLS. The loss of cathepsin C activity in PLS patients may at least partially explain the increased susceptibility to infections, such as cutaneous pyogenic infections and abdominal abscesses. A multidisciplinary treatment approach is essential to the management of patients with PLS, and referrals to appropriate subspecialists should be made as necessary. When a patient presents with transgredient PPK, astute clinicians should be prompted to obtain a complete history and conduct a physical examination, with the most important differentiating factors of PLS being the associated periodontitis and gingivitis and the increased infection

risk. Oral retinoids are the mainstay of treatment of both keratoderma and periodontitis associated with PLS. Due to the risk for pyodermas, recurrent infections, and hepatic abscesses, physicians should have a low threshold for workup of fevers of unknown origin in patients with PLS.

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